

HYPERTHERMIA IN THE TREATMENT OF CANCER

A REVIEW OF THE RADIOBIOLOGICAL BASIS

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SUMMARY

Temperatures in the range 41.5°C to 43.5°C tend to be more damaging to malignant than nonmalignant cells. Where local hyperthermia (41.5°C to 43.5°C) is combined with ionizing radiation, a significant therapeutic ratio may be realized. Total body hyperthermia, alone or combined with other therapeutic modalities, can provide palliation for some systemic malignancies but may not be as effective as local hyperthermia for treating local disease. The influence of hyperthermia on immune mechanisms and the risk of metastatic spread of potential tumor growth stimulation need further investigation. Among other questions needing elucidation before hyperthermia can be considered a standard treatment modality are the time-dose (for heating) relationships to produce an optimal therapeutic ratio and whether the late sequela of combined heat and ionizing radiation may result in an unacceptable risk of patient morbidity.

INTRODUCTION

Radiation therapy may fail to achieve local control of a cancer either because of geographic miss or because of insufficient total dose or time-dose, or both. In the latter case, it may not be possible to deliver a dose of radiation large enough to sterilize all the clonogenic cells because some critical organ in the treated volume, e.g., spinal cord, will receive an intolerable dose. Another possible reason for local failure is the presence of hypoxic foci of tumor cells whose low radiosensitivity results in a significant number of surviving cells when the tolerance dose has been delivered. Another contributing factor could be the inherent capacity of cells from tumors of certain histologies to repair a large proportion of radiation injury following each daily fraction. A number of schemes have therefore been evolved either to increase the radiation sensitivity of the tumor cells or to decrease the sensitivity of the normal tissues in the irradiated volume. Hyperthermia is a technique which has potential for increasing the therapeutic ratio by increasing the radiosensitivity of tumor cells.

Hippocrates described at length the beneficial effects of heat and hot baths in maintaining good health and as a therapeutic regimen for many diseases. It is interesting to speculate whether in Japan, for example, where many people take daily hot baths, there is a connection between this practice and the fact that the national incidence of breast, penile, testicular, and skin cancers is among the lowest in the world. The temperature of these baths ranges from 42°C to 48°C and results in rectal temperatures of approximately 39°C. (See ref. 1.) In Finland, where sauna bathing is practiced, the incidence of testicular and mammary cancer is lower than in neighboring countries where the sauna is not used. (See ref. 2.)

For many years there have been clinical reports indicating that heat has a selectively destructive effect on cancer cells in vivo in comparison with surrounding normal tissues.

Some early clinical reports reviewed by Selawry, et al. (ref. 3) and Cavaliere et al. (ref. 4) include an 1866 account describing histologically proven sarcoma of the face which regressed after high fever associated with syphilis. The reviewers also mentioned a discussion by Coley et al. (ref. 5) of 38 patients with advanced carcinoma who had an association with accidental or deliberate infections. In this series there was complete disappearance of the tumors in 12 cases, and a significant regression in 19 cases. A detailed review of this study was done by Nauts et al. (ref. 6).

In Vitro Studies

When population of cells are exposed to a series of graded doses of X-rays and the percentage of surviving cells counted, the plot of surviving fraction (S) on a log scale against dose on a linear scale yields a dose-effect relationship characterized by an initial shoulder region at low doses and an exponential region at higher doses.

The parameters of this relationship, D_0 , D_q , and n , can be used to define the radiosensitivity of the cells as an estimate of their capacity to repair radiation injury. (See fig. 1.)

If cell populations are incubated at elevated temperatures for different periods of time, the proportion of cells surviving the hyperthermia may be described by using a notation similar to that used for survival after X-radiation.

Figure 2, taken from report by Henle and Leeper (ref. 7), illustrates the response of cells either to X-ray or hyperthermia. The similarities in shape of the dose-response relationships do not imply common mechanism of action, and care must be exercised not to draw unwarranted conclusions by giving the survival characteristics the same interpretation for hyperthermia as for X-ray.

An example of the potentiating effect of hyperthermia on the radiation response of CHO cells is shown in figure 3 taken from a report by Gerner (ref. 8). On the right side of the figure is shown the effect of incubating the cells at temperatures up to 43°C for 1 hour before the X-radiation. The solid circles (upper curve) show the response to radiation at a normal physiological temperature, 37°C. Note that increasing the incubation temperature up to 43°C, a temperature which by itself decreased cell survival to 20 per cent, causes a dramatic increase in radiosensitivity, i.e., by a factor of 2.

As in many new investigative procedures, researchers have adopted a technical jargon. One such expression is the thermal enhancement ratio or TER. This is generally the ratio of a dose of X-ray or drug required to elicit a given effect, compared with the dose of the same agent required to

give the identical effect when combined with hyperthermia.

The term can also be used to indicate the ratio of the slopes of the exponential portions of the dose-response curves when the relationships are determined with and without hyperthermia. It can be considered as analogous to the expressions "dose-modifying factors (DMF)" or OER commonly used in radiation biology.

In the example just stated, the thermal enhancement ratio would be indicated as $TER_{43/1 \text{ hr.}} = \frac{140}{65} = 2.2$.

In this system, the post-irradiation heating did not result in a TER significantly different from that found with pre-irradiation hyperthermia.

At temperatures between 41.5°C and 43°C, a number of systems show tumor cells to be more sensitive to thermal injury than are the normal cells of the same origin. Figure 4, taken from a report by Giovanella *et al.* (ref. 9) is representative of a large body of information indicating this differential thermal sensitivity. The optimum therapeutic advantage probably will be obtained with hyperthermia in the range of 41.5°C to 43°C and that the differential effect between tumor and normal cells may diminish at higher temperatures.

Thermodynamics considerations suggest the possibility that temperatures slightly in excess of 37°C might prove stimulatory to tumor cell growth. Some in vitro studies tend to support this condition (refs. 10, 11, and 12). Above 41.5°C a consistent inhibitory effect can be demonstrated. In applications of hyperthermia to clinical oncology (table 1), temperatures between 41.5°C and 43.0°C are thought to be optimal for differentially sensitizing tumor cells to damage by ionizing radiation.

In some systems the effects of combined X-ray and hyperthermia on cell survival are influenced by the sequence in which the treatments are applied. Gerner *et al.* (ref. 13) found a slightly increased thermal enhancement of radiation damage of CHO cells heated (one hour at 43°C) immediately after irradiation, but noted an opposite response for HeLa cells. Van der Schueren 1975 (ref. 14), using a cell line derived from ureteral tissue, found a greater thermal enhancement of cell kill by heating near the end of, or immediately following, exposure to X-radiation.

Sapareta *et al.* 1976 (ref. 15) compared the effect of heating (42.5°C or 45.5°C) CHO cells during and up to 120 minutes before or after a 500 rad dose of X-radiation. The data clearly showed that the potentiating effect of heat on cell death was greatest when the radiation was delivered early during the heating interval. There was a rapid loss of thermal effect if the radiation was given after the heating. Using radiation damage to mouse skin as the criteria of response, Field *et al.* (ref. 16) found that heating (42°C or 43°C for 1 hour) at intervals up to 2 hours before X-radiation yielded a significant thermal enhancement. The thermal enhancement was lost rapidly if the heat was given after the irradiation.

Gillette and Thrall in 1975 (ref. 17) found thermal potentiation of X-ray

damage to mouse mammary carcinoma to be highest when the heat was applied immediately after irradiation. Based on extensive clinical experience, Holt (ref. 18) concluded that the TER is maximum when the hyperthermia was delivered before the irradiation. Overgaard and Overgaard (ref. 19) using a solid tumor in mice find that the potentiating effect of hyperthermia on the response of the tumor to X-radiation was independent of the sequence in which the treatment were applied up to an interval of 24 hours.

It seems reasonable to assume that the maximum potentiation of radiation damage by hyperthermia would occur when the interval between treatments was short. In the application of hyperthermia to clinical radiation oncology, the sequence will probably be determined by the treatment logistics of the department at least until the basis of selecting one sequence over another is more clearly evident. The expression of thermal damage is not limited to the potentiation of X-ray responses. Figure 5 (ref. 19) shows the interaction of hyperthermia and drugs when temperatures of 42°C produce very large decreases in cell survival. Figure 6 (ref. 20) shows the response of population of tumor cells which were treated in vivo but assayed in vitro. These data indicate that both in vivo and in vitro hyperthermia enhances the effectiveness of these cytotoxic agents.

There are no data available at this time showing the effect of multidrug chemotherapy and hyperthermia. Such studies might yield valuable information.

Before the potentiating action of hyperthermia can be exploited as part of a therapeutic regimen, it is necessary to establish whether a significant therapeutic ratio can be achieved.

The therapeutic ratio is essentially a cost-benefit assessment. Figure 7 illustrates this relationship. It is determined by estimating the damage done to the tumor, i.e., regression in size or palliation of symptoms compared with the damage done to the normal tissues in the irradiated volume.

Table 2, based on the work of Robinson in Baltimore (ref. 21) shows that although both the TER for tumor and normal tissues increase with temperature, the TER for tumors increases faster than that for normal tissue (skin). This observation indicates that a significant therapeutic ratio can be achieved. There are data indicating that the differential sensitivity of normal and tumor cells is absent at higher temperatures.

Radiation and the Oxygen Effect

One of the problems confounding the radiotherapist is the fact that hypoxic cells have a reduced radiosensitivity. If the radiosensitivity of cells made severely hypoxic during irradiation is compared with those fully oxygenated, the sensitivities characteristically differ by a factor of between 2 and 3. This ratio is designated as the oxygen enhancement ratio or the OER. In a number of systems, hypoxic cells have been shown to be more sensitive to thermal injury than are toxic cells. In many systems, therefore, it is possible to demonstrate a significant reduction in OER by hyperthermia. This fact is potentially of very great significance, since it may increase the chance of control or provide palliation of bulky local disease

which would otherwise be impossible. This is demonstrated by table 3 taken from a report by Robinson (ref. 21). Other investigators (ref. 22) have also observed an enhanced TER for hypoxic cells.

Whole Body Hyperthermia

About 1913, A. A. Strauss used surgery and hyperthermia to treat carcinoma of the rectum and colon, with excellent results (ref. 23). By 1956 he had treated 250 such patients, and long-term follow-up indicated results comparable with, or superior to, any therapy then available (ref. 24).

Pettigrew et al. (refs. 25 and 26) treated a number of terminal-stage cancer patients with total-body hyperthermia (41°C to 42°C) and occasionally combined this treatment with chemotherapy. In all cases the patients were no longer treatable by conventional therapeutic modalities. For those treated, hyperthermia alone produced a significant regression in sarcomas and in tumors of the gastro-intestinal tract. Breast and genito-urinary tumors responded poorly. All patients with pain or bleeding experienced palliation of these symptoms. Figure 8 taken from a report by Stolwijk (ref. 27) shows the probably range of temperatures that might be tolerated for whole body hyperthermia. It is unlikely that a temperature in excess of 43°C could be tolerated for more than a few minutes without significant risk of severe damage. Most clinical series have therefore attempted to achieve a core temperature in the range of 40°C to 42.5°C .

As with any therapy whose mechanism of action is not well understood there are many questions that remain to be resolved. It seems likely that temperatures only slightly above the normal physiological range may stimulate tumor growth rather than inhibit it. There are some experimental data which support this possibility (ref. 28). There is some indirect evidence from animal studies that whole body hyperthermia (to 40°C temperature elevation) may temporarily suppress immune mechanisms and perhaps potentiate metastatic spread. Figures 9 and 10 taken from a report by Dickson (ref. 12) illustrate this concern. Animal studies (refs. 29 and 30) indicate an increased risk of metastatic spread with whole body hyperthermia. Evidence for an increased risk from local hyperthermia has not been clearly demonstrated. The effectiveness of local compared with total body hyperthermia is illustrated by figure 11 taken from a report by Dickson and Muckle (ref. 30). This may not be critical consideration in palliative therapy for systemic disease.

Regional Hyperthermia by Perfusion

A number of investigators have used hyperthermic perfusion of extremities to treat disease when local spread was suspected. The data in table 4 from a report by Stehlin et al. (ref. 31) show the results of hyperthermia perfusion on melanoma lesions of the extremities. The data shows hyperthermia resulted in an increased incidence in regional control and palliation of disease.

Cavaliere et al. (ref. 4) reported tumor regression in 15 of 22 patients treated with heated perfused blood for sarcomas and melanomas of the extremities. In the Proceedings of the International Symposium on Cancer

Therapy by Hyperthermia and Radiation, Cavaliere et al. (ref. 32) reviewed their experience in using hyperthermic perfusion to treat 111 patients with advanced tumors of the extremities: 5, squamous-cell carcinoma; 27, osteogenic sarcoma; 28, other sarcomas; and 51, melanoma. In some instances, chemotherapeutic agents were incorporated into the perfusate. Most of these patients subsequently underwent amputation of the affected limb. Although there was a variety of temperatures, durations, and other conditions, there was no doubt that initial tumor response and NED survival for comparable stages of clinical disease treated without hyperthermia (historical controls) were consistently improved by the use of hyperthermia.

Hall et al. (ref. 33) perfused the bladders of 32 patients suffering from carcinomas of the urinary bladder with solutions at temperatures between 41.5° and 45°C. There was substantial tumor regression in 26 of the patients and complete tumor regression in 4.

Cockett et al. (ref. 34) reported a reduction in tumor size following local hyperthermia and regional radiotherapy in 7 elderly patients with incurable carcinomas of the bladder. In contrast, Lunglmayr et al. (ref. 35) reported that local hyperthermia combined with chemotherapy failed to offer any substantial gain in the treatment of low stage vesicle papillomas because of a high rate of complications which followed this treatment.

Local Hyperthermia

Selawry et al. (ref. 3) made reference to more than 30 published clinical series in which a wide spectrum of tumors were treated by various combinations of X-ray and hyperthermia. All these reports noted the potentiating effect of hyperthermia on radiation response of the tumor, although uncertainties in radiation dosimetry and temperatures measurements made more precise comparisons of response impractical.

Holt (ref. 18) treated patients by means of a device consisting of 12 RF generators operating at 433.92 MHz and placed in a circular configuration, with the patient sitting or standing in the center of the cylindrical array. For most patients the RF irradiation was combined with X-ray therapy or chemotherapy. The report indicated that 363 patients with advanced disease were treated. The author gave no details concerning tissue temperatures, duration of the radiofrequency treatments, or intervals between RF and X-ray treatments (H + Rx). He concluded that RF radiation produced significant enhancement of therapeutic ratio for patients receiving X-ray therapy. Hornback et al. (ref. 36) using a similar technique reported a significant enhancement of radiation response for patients with a wide range of malignancies.

Brenner (ref. 37) combined hot air jets and microwave (2450 mc/sec) to induce local hyperthermia which they used with orthovoltage radiation to achieve impressive tumor regression in 6 patients. LeVeen (ref. 38) reported a series of 21 patients treated by inducing local hyperthermia in tumors through use of a radio frequency generator operated at 13.56 MHz. In all cases there was significant tumor regression.

Johnson (ref. 39) reported results of a pilot clinical trial to assess the therapeutic ratio when X-radiation was combined with local hyperthermia to treat patients with multiple superficial lesions, i.e., up to 2 cm. in depth. The lesions were heated to 41°C to 42.5°C with 915 MHz microwaves for periods of 1½ to 2 hours. Heating alone produced no damage to the normal skin. The thermal enhancement ratio (TER) for irradiated normal skin was 1.2 to 1.3. Heating during and immediately after irradiation produced the maximum response of tumor and normal tissues. The data are not yet sufficiently complete to make possible an estimate of the therapeutic ratio.

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TABLE 1.

<u>37.0 - 38° 0° C</u>	<u>39.0° - 41° 0° C</u>	<u>41.5 - 43.0° C</u>	<u>43.5 - 46.0° C</u>
Normal	Potential	Differential	Loss of diff-
Temperature	Stimulation	Thermal damage	erential for
		to tumor cells	thermal damage
			to tumor cells

Table - 1 shows the probable useful range of temperatures for tumor sensitization in therapeutic oncology.

TABLE 2.

TEMP. (°C)	SKIN RESPONSE		TUMOR RESPONSE		TUMOR T.E.R. SKIN T.E.R.
	T.E.D. _{.50%} (rads)	T.E.R.*	T.C.D. _{.50%} (rads)	T.E.R.*	
37.5	2522	1.00	5250	1.00	1.00
41.0	2122	1.18	3800	1.38	1.17
42.5	1506	1.67	1910	2.74	1.64
43.0	1223	2.06	1230	4.27	2.06

A comparison of the thermally induced increase in radiation sensitivity of C3H mammary tumors and normal mouse skin. T.E.R. (Thermal Enhancement Ratio) is defined here as the ratio of the dose required to produce 50 percent response at 37.5°C to the dose required to elicit the same response at a specified elevated temperature.

TABLE 3.

TEMP (°C)	ANOXIC	OXYGENATED	O.E.R.
37.5	0.385 ± .022	0.947 ± .046	2.46 ± .18
41.0	0.406 ± .017	1.16 ± .09	2.86 ± .25
42.0	0.68 ± .06	1.86 ± .017	2.72 ± .35
42.5	1.07 ± .06	1.81 ± .18	1.69 ± .14
43.0	1.93 ± .09	2.66 ± .12	1.38 ± .09
43.5	2.24 ± .17	2.09 ± .33	0.87 ± .16

The differential effect of hyperthermia on anoxic and oxygenated mouse bone marrow cells. The main body of the table gives slopes of both anoxic and well-oxygenated cells in units of 10^{-2} /rad. Treatment times were for one hour except for the highest treatment temperature, 43.5°C. for which a shorter time of 20 minutes was used. The O.E.R. values were calculated from the ratio of survival curve slopes.

TABLE 4.

COMPARATIVE DATA ON STAGE IIIA
METASTATIC MELANOMA OF THE EXTREMITIES

	<i>No Heat</i> (1951-65)	<i>Heat</i> (1967-74)
Number of patients.....	27	30
Female.....	13	24
Male.....	14	6
Extremity involved		
Upper.....	7	2
Lower.....	20	28
Regional nodes proved negative		
microscopically.....	22/27, 81%	17/30, 56%
Patients with more than one recurrent (meta-static) nodule.....	21, 78%	23, 77%
Radical amputation....	8/27, 30%	0
Patients perfused.....	21/27, 78%	30/30, 100%
Perfusion drug.....	Alkeran	Alkeran
Average dose		
Lower extremity.....	1.2-1.6 mgm./kgm.	0.9 mgm./kgm.
Perfusion time.....	45-120 mins.	45-120 mins.
Skin temperature.....	86-90°F.	102-105°F.
Muscle temperature....	92-95°F.	102-104°F.
Five year survival rate		
Males and females....	22.2%*	76.7%†
Females only.....	13, 30.7%*	24, 88.7%†

*Crude.

†Berkson-Gage.

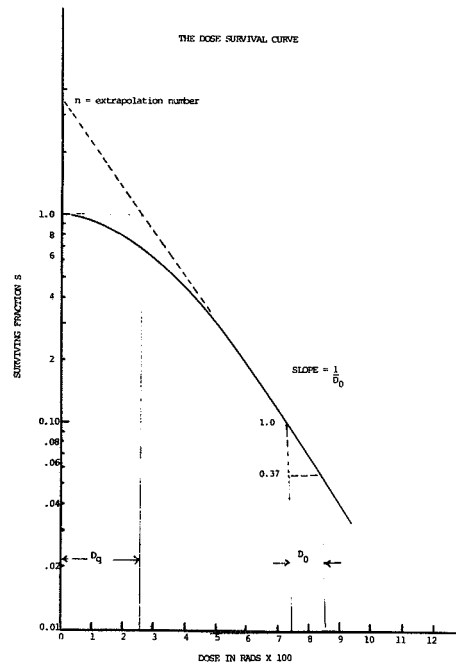
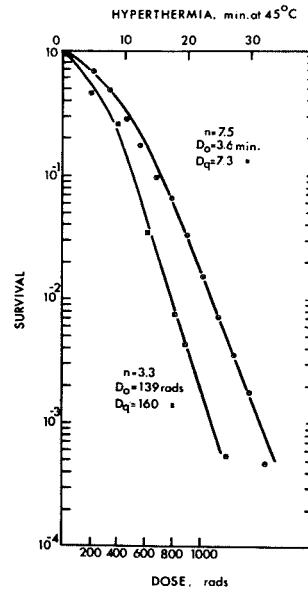


Figure 1.



Fractional survival (corrected for cellular multiplicity) of cells heated for various times at 45°C (upper curve, ●) or X rays (lower curve, ■). In this and the following figures curves were fitted to the data points by eye. Standard errors were smaller than the plotted points.

Figure 2.

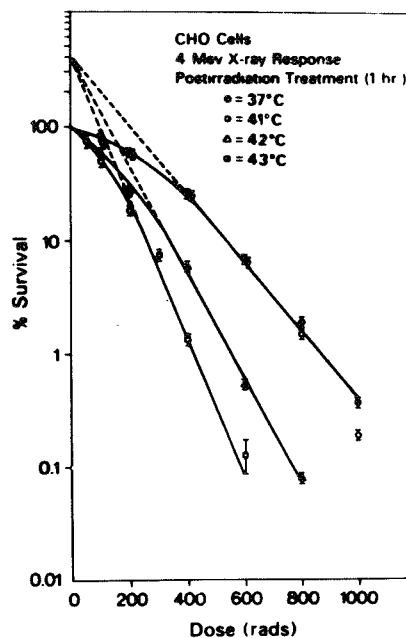
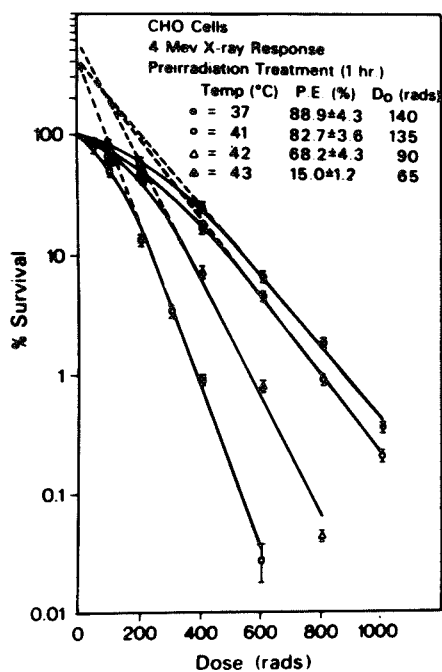
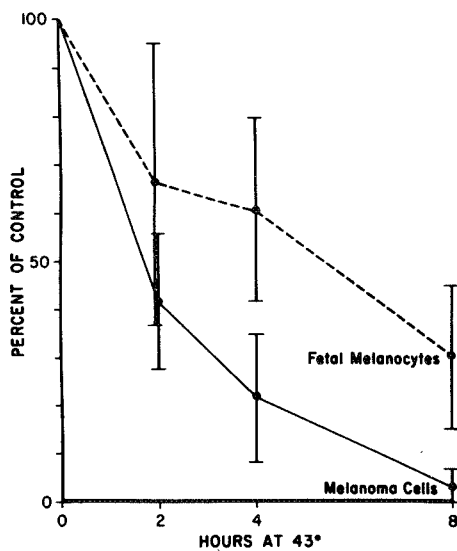
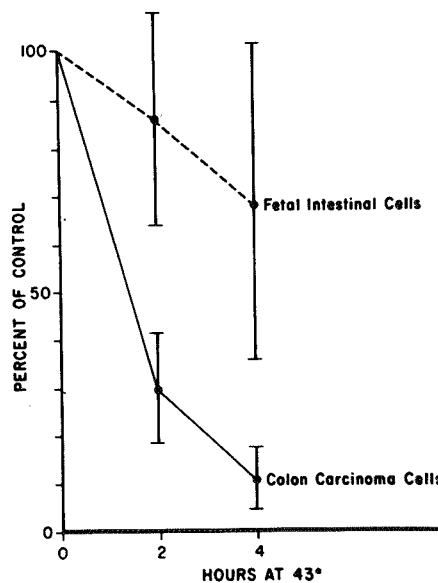


Figure 3.

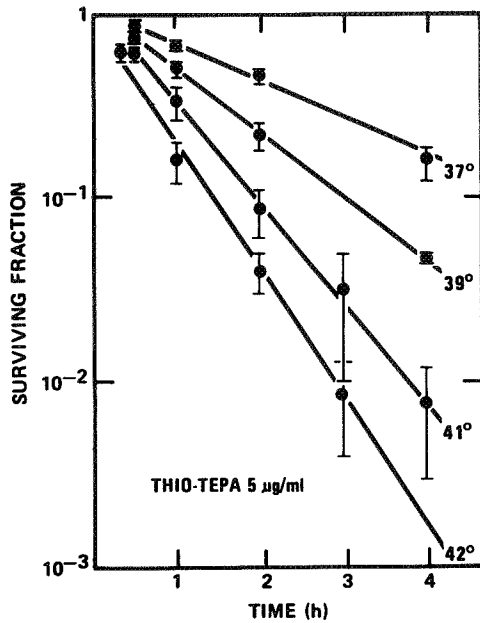


The percentage of surviving melanoma cells and fetal melanocytes as a function of the duration of exposure to 43° (mean ± S.D. of pooled experiments given). Data from Table 1. At 4 and 8 hr, the difference in heat sensitivity between fetal melanocytes and melanoma cells is statistically significant, $p < 0.05$ and $p < 0.01$, respectively.

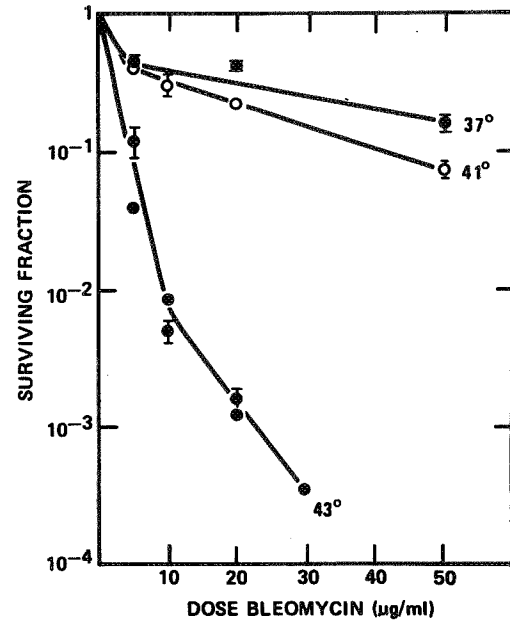


The percentage of surviving colon carcinoma cells and fetal intestinal cells as a function of the duration of exposure to 43° (mean ± S.D. of pooled experiments given). Data from Table 2. At 2 and 4 hr, the difference in heat sensitivity between fetal intestinal cells and colon carcinoma cells is statistically significant ($p < 0.01$).

Figure 4.

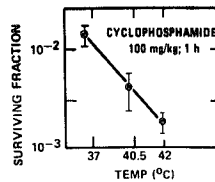


Effect of elevated temperature on the killing of V-79 Chinese hamster cells by thio-tepa (1).

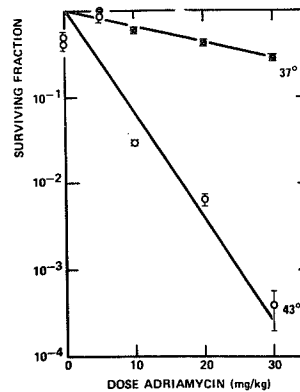


Effect of elevated temperature on the killing of HA1 Chinese hamster cells by bleomycin (6).

Figure 5.



Effect of elevated temperatures on the killing "in vivo" of EMT-6 tumor cells by cyclophosphamide (Mann, unpublished data).



Effect of 43°C on the cell killing "in vivo" of EMT-6 tumor cells by adriamycin (7).

Figure 6.

THERAPEUTIC RATIO (T.R.)

$$= \frac{\text{Effect on Tumor}}{\text{Effect on Normal Tissue}}$$

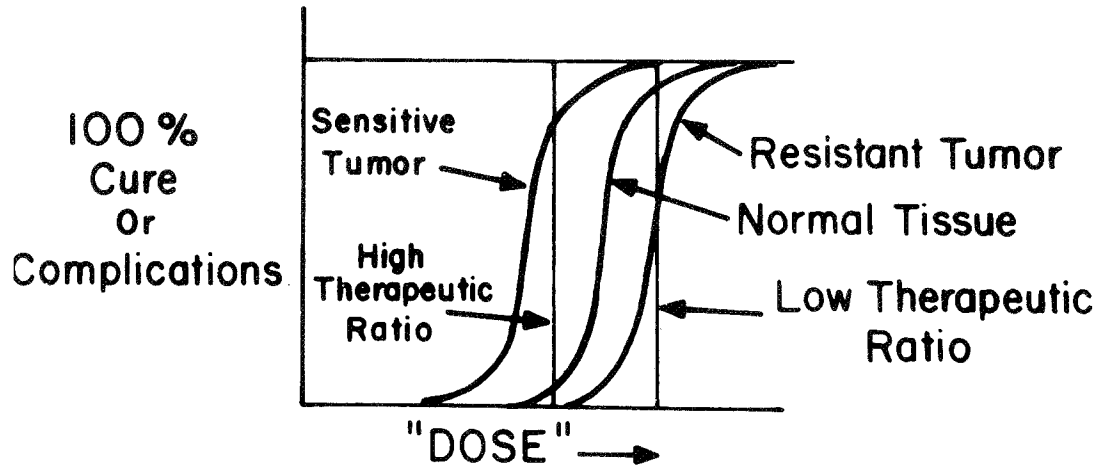
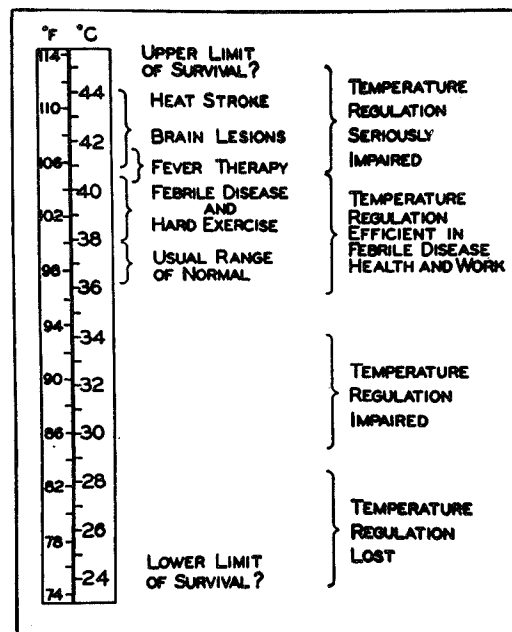
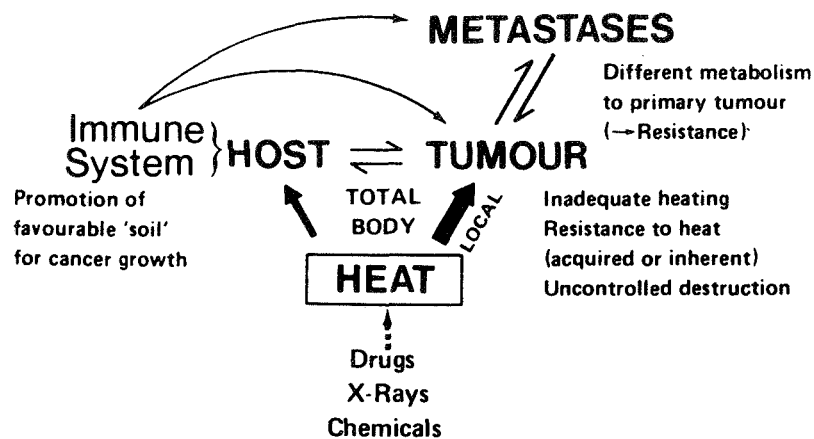


Figure 7.



Approximate range of internal body temperatures in man with associated responses or consequences.

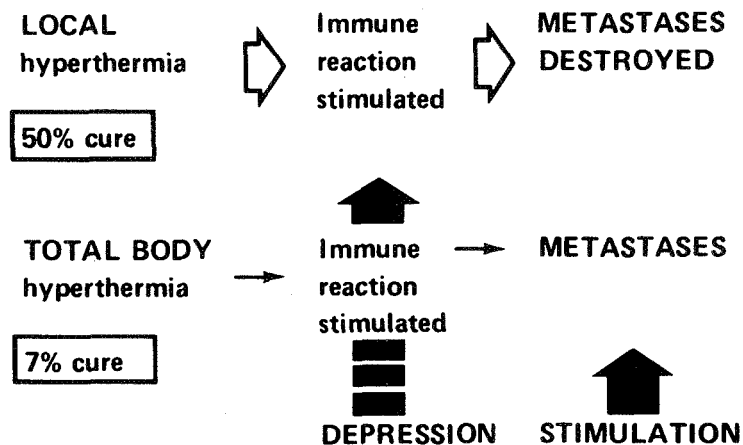
Figure 8.



Host-tumor-therapy triad interrelationships govern therapeutic outcome. The possible hazards involving the host and the tumor when heat constitutes the treatment are indicated; 'potentiators' of heat (broken arrow) are viewed as affecting both these components.

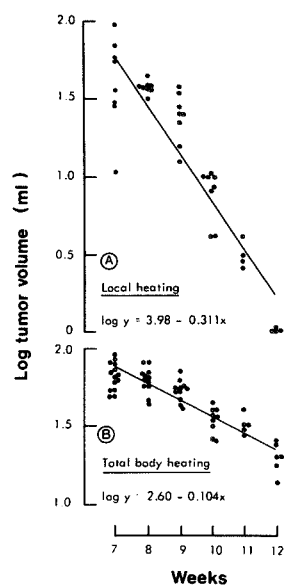
Figure 9.

RABBIT VX₂ SYSTEM



Scheme to illustrate the difference in results obtained in treatment of the VX₂ carcinoma by local heating and total body heating in terms of postulated effects on the host immune system.

Figure 10.



Regression lines fitted to log tumor volume measurements from the 7th week following tumor inoculation. Local hyperthermia to the tumor-bearing limb (A), or total-body hyperthermia (B), was applied on Days 35, 36, and 37 after cell inoculation. The individual tumor volumes for all experiments shown in Chart 3 have been plotted, and the equation to the regression line in each case is given.

Figure 11.

Questions and Answers Following Baker's Paper

Singh: Why did you not go beyond 43°C ?

Baker: That last study was not my particular study; but the reason for not going beyond 43°C is that as you start to increase the temperature in excess of 43°C , you begin to get cell killing and you lose the sensitizing effect of the radiation. The idea of the radiation is to increase the maximum potential very quickly. At higher temperatures you do not need radiation; you kill all the cells without it.

Merz: What were the drugs?

Baker: The drugs were cyclophosphamide and adriamycin.

Merz: What were the two before?

Baker: The two before were bleomycin and thio-tepa.

Singh: Dr. Baker, how is the heating done in the studies by Dr. Holt, for example?

Baker: Dr. Holt uses a circular array of some 12 radio-frequency generators operating at 414 megahertz. This radio frequency will heat a very large volume of tissue. The frequency is readily absorbed so that there is very effective heating. Dr. Pettigrew uses a liquid molten paraffin bath. He bags the patient in a plastic bag, intubates him, and uses spinal anesthesia. He depends on the heat of fusion of the paraffin as it goes from the liquid to the solid state, in order to produce the proper temperature to heat the patient. His patients are kept under these conditions for 6 to 14 hours, so it is a simple system. The German group uses infrared radiation for their total body hyperthermia. The group in Colombia at Bogota uses Coley's toxin, or its local equivalent, for inducing systemic hyperthermia. Other groups use different frequencies of radiation for local hyperthermia. The RTOG protocol calls for the use of 915 megahertz. We have tried both 2450 megahertz, and more recently 27 megahertz, radiation for inducing local hyperthermia.

E. Long: I did not catch, and perhaps you had it there, the amount of time that locally it was heated, or systemically it was heated, versus the amount of time for the X-ray radiation.

Baker: It turns out that as long as you are in a temperature range between 41°C and 43°C the effectiveness of your thermal enhancement -- or if you like, the thermal enhancement ratio -- is directly related to the duration. So you would, if you have a 41°C hyperthermia, like to sustain it for as long as you could. In this circumstance we are talking about some 3, 4, 5, or more hours. On the other hand, if you can get to a temperature of around 43°C , then probably 1 to 2 hours will give you the maximum therapeutic ratio.

E. Long: How does that compare to the length of time for the X-rays?

Baker: Well, the X-rays are conventionally delivered at conventional dose rates of perhaps 100 to 250 rads per minute. If your fraction size is as we have usually used, somewhere between 300 and 500 rads per fraction, then the duration of your radiation would be somewhere between 3 and 5 minutes. Yes, Dr. Atkinson.

Atkinson: Don, when I came in, you had a slide up of therapeutic ratios; and I did not quite get the story that went with them. Was that on in vitro or in vivo measurements? How was it measured?

Baker: I am not sure which slide we were talking about. I think this was an in vivo mouse mammary carcinoma system.

Atkinson: How was the damage to the normal tissue measured?

Baker: I understand, yes. This was the damage done to the skin. This was a skin reaction graded 1, 2, 3, etc., compared to local control of the mammary tumor. This was the ratio.

Singh: The temperatures that you are talking about are the entire mouse temperatures. They are not the temperatures of the region you are treating. Is that right?

Baker: Well, in some of the work I was referring to, we were talking about systemic hyperthermia and the temperature of the whole body. In other cases, it was local hyperthermia and the temperature of the tumor, or the volume that you are particularly concerned with radiating.

Singh: And that was that low for this treatment? It did not go higher?

Baker: No, no. Once you get higher than about 43° C, you begin to produce such an increase in sensitivity of the normal tissues that your therapeutic ratio is lost and there is no advantage.

Beebe: In these, did you measure the temperature of the tumor and of the tissue separately?

Baker: Yes. That is the way that we always try to do it. There are some considerable difficulties with making that measurement, as you can well imagine, because there are local areas where there is circulation, and for other technical reasons and physiological reasons, there are temperature gradients that exist.

Rosato: Dr. Baker, the incidence of cancer in undescended testes is known to be seven- or eight-fold greater than the normal situation. The assumption unproven is that this is the result of the exposure of the testicle to a higher temperature over a longer period of time in its intra-abdominal

position. Is there any literature, or any caveats, about the possible carcinogenic effect of hyperthermia, especially when applied over a long period of time?

Baker: No. This is information we do not have, but there are a couple of studies in which this is addressed indirectly. If you take an animal, a rat for example, and place him in a chronic, low temperature, 3 or 4 degrees above freezing, he compensates for this by increasing his metabolic rate. In fact, he will double it. He will live his whole life at twice its normal rate. Not only that, but he will compensate by increasing his core body temperature. His core body temperature will go up about 2 degrees, so now you have an animal whose core temperature is up 2 degrees, and it is up 2 degrees for the rest of his life. Now, the incidence of tumors in those animals is dramatically less, not more, so that this leaves the question still very much unanswered. But that is about the only comparison I can make for you.